REMARKS

The present invention relates to isolated marrow stromal cells ("MSCs") for use in treatment of a central nervous system ("CNS") disease, disorder or condition in a human patient. The invention includes methods directing the *in vivo* differentiation of isolated marrow stromal cells in the CNS of a human patient.

The above-captioned application was filed as a continuation of U.S. Application No. 09/028,395, now issued as U.S. Patent No. 6,653,134. By way of Preliminary Amendment filed concomitantly with the instant application on June 27, 2003, original claims 19-20 were canceled. By way of a Second Preliminary Amendment filed October 10, 2003, claims 1, 9, 11 and 16 were amended to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Claims 1-18 are currently pending in the application. Claims 9-15 have been withdrawn from consideration as being drawn to non-elected inventions. Therefore, claims 1-8 and 16-18 are currently under consideration. Claim 1 has been amended to delete the phrase "directing differentiation," and replaced it with the term "differentiating." Support for this amendment is found in the specification on page 14, lines 11 through 15. Thus, no new matter has been added by way of this amendment.

Objections to Drawings

The Examiner has objected to Figure 6. Specifically, the Examiner contends that Figure 6 does not clearly identify which sections pictured in Figure 6 correspond to day 4, 14, 30, or 72, as disclosed in the specification. It appears that the Examiner is requesting that Figure 6 be amended to label the appropriate sections with the corresponding day. Applicants traverse the Examiner's objection to Figure 6 for the following reasons.

Applicants do not understand the Examiner's allegation that Figure 6 fails to show what is described in the specification. As recited in the specification, Figure 6 is a series of line drawings of rat forebrain, illustrating the migration of marrow stromal cells (MSCs) through the brain following cell infusion. Specifically, Figure 6 is a **composite** from brains examined at 4, 14, 30 and 72 days after cell infusion. As defined in the Merriam-Webster Online Dictionary, the term "composite" refers to combining the typical or essential characteristics of individuals making up a group; specifying a range of values for one or more statistical parameters. It

appears that the Examiner has overlooked the fact that Figure 6 is a composite or otherwise a summary highlighting the observed migration of the cells.

A more detailed discussion of Figure 6 is found in the specification beginning on page 52, the specification recites, "donor cells were found in multiple areas of the brain, including the contralateral cortex (FIG. 6). The cells persisted in the sites to which they migrated. The heaviest concentration of cells was found around the rostrocaudal axis in the striatum and along the corpus callosum. There were fewer cells in the cerebral cortex. Clusters of labeled cells were consistently observed in the temporal lobe regions at all time points examined. At day 72, fewer cells were found in the outlying cortical regions, an observation consistent with the apparent decrease in cell number between day 30 and 72 (Table 5)." Therefore, when viewed in light of the specification in its entirety, including the Tables and the detailed descriptions thereof, is abundantly clear that Figure 6 is a schematic of a composite of the migration of donor cells after infusion. Thus, there is nothing unclear about Figure 6. Applicants respectfully request that the objection to this figure be reconsidered and withdrawn.

Amendment to the Application to claim priority under 35 U.S.C. § 119(e)

By way of Preliminary Amendment filed concomitantly with the instant application on June 27, 2003, the specification was amended to properly claim priority to the prior applications. Applicants respectfully submit that the priority was correctly claimed on the transmittal form filed with the present application on June 27, 2003, as well in the Preliminary Amendment filed with the application. Further, Applicants respectfully point out to the Examiner that the Filing Receipt indicates that the USPTO recognized that the present application is a continuation of U.S. Application Ser. No. 09/028,395, filed February 24, 1998, which is a continuation-in-part of PCT Application No. PCT/US96/04407, filed on Mar. 28, 1996, which is a continuation of U.S. Application Ser. No. 08/412,066, filed on March 28, 1995.

The Examiner contends that the priority claim is objected to because the specification makes reference to PCT Application No. PCT/US96/04407, U.S. Application No. 08/412,066 and U.S. Application No. 09/028,395 without stating the publication number/issued patent number (i.e. WO/ 96/30031, U.S. Pat. No. 5,716,616 and U.S. Patent No. 6,653,134, respectively). Applicants assert that according to 37 C.F.R. § 1.78(a)(2), all that is needed to comply with 37 C.F.R. § 1.78(a)(2) is reference to an international application number and

international filing date and indicating the relationship of the applications. There is no requirement for citation of the publication number/issued patent number of the prior applications.

As recited in 37 C.F.R. § 1.78(a)(2), any nonprovisional application claiming the benefit of one or more prior-filed copending nonprovisional applications or international applications designating the United States of America must contain or be amended to contain a reference to each such prior-filed application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications.

The Examiner's objection to the priority claim for not stating the publication number/issued patent number corresponding to the appropriate application is improper. In any event, Applicants have amended the specification to update the status of U.S. Application Nos. 09/028,395 and 08/412,066 as being now issued as U.S. Patent Nos. 6,653,134 and 5,716,616, respectively.

In addition to the objection to the priority claim on the grounds of formal requirements, the Examiner has also denied priority to PCT Application No. PCT/US96/04407, U.S. Application Ser. No. 08/412,066 (U.S. Patent No. 5,716,616), and U.S. Provisional Application No. 60/006,627 because the Examiner contends that these applications do not provide a disclosure commensurate with the requirements of 35 U.S.C. § 112, first paragraph. The Examiner is of the opinion that the prior applications do not support the claimed invention as encompassed in the pending claims. The Examiner asserts that this application only has priority to U.S. Application No. 09/028,395 (U.S. Patent No. 6,653,134).

Applicants respectfully point out that MPEP § 201.08 provides: "Unless the filing date of an earlier application is actually needed, for example, in the case of an interference or to avoid an intervening reference, there is no need for the examiner to make a determination in a continuation-in-part application as to whether the requirement of 35 U.S.C. § 120 (benefit of earlier filing date in the U.S.) is met." In fact, the Examiner has not cited any intervening reference.

Applicants submit that the priority was correctly claimed at the time of filing the above-captioned application and therefore request that the objection to the priority claim be reconsidered and withdrawn.

Rejection of claims 1-8 and 16-18 pursuant to 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-8 and 16-18 under 35 U.S.C. § 112, first paragraph as lacking written description. The Examiner is of the opinion that the specification does not sufficiently describe a method of directing differentiation of a marrow stromal cell into a neural cell in a human patient. Applicant respectfully traverses this rejection for the following reasons.

Applicants respectfully submit that they have indeed provided sufficient written description as required by the applicable law. In the landmark case of *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), the Court of Appeals for the Federal Circuit traced the development of the written description requirement under 35 U.S.C. §112, first paragraph. The *Vas-Cath* Court, in a unanimous opinion, noted approvingly that in a written description analysis, "[t]he primary concern is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Vas-Cath*, 19 USPQ2d at 1116 (quoting *In re Wertheim*, 191 USPQ 90, 96 (C.C.P.A. 1976)) (emphasis added). After discussing the policy reasons underlying the requirement, the Court set forth the standard for the written description requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use;" the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. . . . The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."

Vas-Cath, 19 USPQ2d at 1117 (emphasis added) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). Therefore, it is well-settled that the knowledge of those skilled in the art informs the written description inquiry.

In determining the sufficiency of support in a disclosure with respect to the written description requirement, "it is not necessary that the application describe the claimed invention in *ipsis verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him." *In re Edwards*, 196 USPQ 465, 467 (C.C.P.A. 1978) (citing *In re Lukach*, 169 USPQ 795 (C.C.P.A. 1971); *In re Driscoll*, 195 USPQ 434 (C.C.P.A. 1977)). More recently, in

In re Kaslow, 217 USPQ 1089, 1096 (Fed. Cir. 1983), the Court of Appeals for the Federal Circuit, citing *In re Edwards*, emphasized:

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language. (Emphasis added).

In addition, in *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit pointed out that literal support is not required in order to satisfy the written description requirement:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. For example, in *Ralston Purina Co. v. Far-Mor-Co., Inc.*, 227 USPQ 177, 180 (Fed. Cir. 1985), the trial court admitted expert testimony about known industry standards regarding temperature and pressure in "the art of both farinaceous and proteinaceous vegetable materials." The effect of the testimony was to expand the breadth of the actual written description since it was apparent that the inventor possessed such knowledge of industry standards of temperature and pressure at the time the original application was filed. (Emphasis added).

Therefore, it is clear that the invention need not be described in *ipsis verbis*, *i.e.*, literally, for purposes of the written description requirement under 35 U.S.C. §112, first paragraph. Rather, what is needed is that the skilled artisan understand, based upon the disclosure in the specification as filed and the knowledge imputed to the skilled artisan at the time the specification was filed, that the inventor had possession of the claimed subject matter.

The Examiner is of the opinion that the specification as filed does not contemplate differentiation of a stromal cell *in vivo*. Specifically, the Examiner points out that the specification defines the phrase "directing differentiation," to mean the induction of a differentiated phenotype in an undifferentiated cell by coculturing the undifferentiated cell in the presence of a substantially homogeneous population of differentiated cells. However, Applicants point out that the specification indicates that the phrase "directing differentiation," **should** be construed to mean the induction of a differentiated phenotype in an undifferentiated cell by coculturing the undifferentiated cell in the presence of a substantially homogeneous population

of differentiated cells. The specification does not indicate that "directing differentiation" must be construed to be coculturing of the cells.

Throughout the specification, there is ample support for the *in vivo* differentiation of stromal cells into cells of the central nervous system. For example, in lines 11 through 15, on page 14, the specification indicates that the present invention is based on the discovery that MSCs when infused into a mammal brain, engraft, migrate, and differentiate into cells of the central nervous system. Example 7 also teaches neurotransplantation of MSCs. Nowhere in Example 7 is there a requirement that the MSCs be differentiated *in vitro* prior to implantation of the cells into a recipient.

Applicants respectfully submit that the skilled artisan would have understood, based upon the disclosure provided in the specification as filed, that the inventors had possession of the invention claimed in amended claim 1. Claim 1 has been amended herein to delete the phrase "directing the differentiation." Claim 1 recites a method of differentiating an isolated stromal cell into a neural cell in a human patient suffering from a disease, disorder or condition of the central nervous system, the method comprising obtaining a bone marrow sample from a human donor, isolating stromal cells from the bone marrow sample, and administering the isolated stromal cells to the central nervous system of the human patient. Support for this claim is in the as-filed specification.

Accordingly, Applicants respectfully submit that the Examiner's written description rejection of claims 1-8 and 16-18 has been overcome, and as such, Applicants request that the rejection be reconsidered and withdrawn.

Rejection of claims 1-8 and 16-18 pursuant to 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-8 and 16-18 under 35 U.S.C. § 112, first paragraph, for lack of enablement for apparently containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner contends that the claims encompass *in vivo* differentiation of marrow stromal cells into cells of the central nervous system as a means of cell and/or gene therapy to treat a disease or disorder of the central nervous system. Specifically, the Examiner is of the opinion that Applicants would have had to perform "undue experimentation" to make and/or use the claimed invention. Applicants respectfully submit that the claimed invention is

enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph, for the following reasons.

It is well-settled that an Applicant need not have actually reduced the invention to practice prior to filing. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

The Examiner cites Barley et al. (2003, Expert Opin. Biol. Ther. 3:541-549), Savitz et al. (2003, J. Cardiovasc. Nurs., 18:57-61), and Horn et al., (2004, Molec. Ther., 10:417-431) to support his arguments that cell and gene therapy are unpredictable art, and therefore the present invention lacks enablement and requires undue experimentation.

Specifically, the Examiner contends that the specification does not disclose the route of administration and the number of cells required for a therapeutic effect. Applicants point out that the specification amply teaches methodologies for using MSCs. For example, the specification teaches that MSCs are administered to a mammal so that the cells differentiate following introduction to the central nervous system (page 15, lines 4-18). In addition, the specification demonstrates the successful reduction to practice in that Example 7 discloses the implantation of MSCs in the brain (page 47, line 8, to page 53, line 12). Thus, the skilled artisan, based upon the teachings of the invention, would have been able to implant the cells and practice the methods of the invention without under experimentation. Accordingly, the skilled artisan would have understood that the route of administration also depends on the site of injury, the disease being treated, and can determine the route of administration without undue experimentation.

With respect to the number of cells to be administered, one skilled in the art would recognize, based upon the teachings of the specification as filed, that initial clinical trials could be performed by simple adjusting cell numbers used in the animal model disclosed by factoring in the weight and age of the patient as routinely performed in the art. Also, standard formulas for testing increasing dose levels are used in FDA prescribed Phase I or clinical trials and the skilled artisan routinely determined such dosages such that doing so would not be undue experimentation.

The Examiner also argues that at the time of filing, the state of the art taught that the therapeutic effectiveness of the cells was neither routine nor predictable. Applicants submit post-filing references to demonstrate further reduction to practice (Kopen et al., 1999, Proc. Natl. Acad. Sci. 96:10711-10716; Hofstetter et al., 2002, Proc. Natl. Acad. Sci. USA 99:2199-2204; and Chopp et al., 2000, NeuroReport 11:3001-3005). These references demonstrate that MSCs can provide a therapeutic effect following administration into a mammal suffering from a disease, disorder or condition of the CNS. Without wishing to be bound by any particular theory, following administration to a mammal, MSCs can provide a therapeutic effect by either differentiating into cells of the CNS (e.g. astrocytes, oligodendrocytes and neurons) and/or the MSCs can provide a microenvironment for endogenous cells of the CNS to give benefit to the recipient.

The post-filing references demonstrate that the invention has been further reduced to practice whereby the same methods as those included in the application were utilized to arrive at the results predicted in the as-filed application. These references provide evidence that the disclosure of the as-filed specification enables the claimed invention, and argues against the Examiner's assertion that the specification lacks enablement regarding the present invention. These references are not prior art to the present application, but rather represents post-filing reduction to practice of the present invention. The contents of these references are more fully discussed below.

Kopen et al. demonstrates that MSCs can differentiate into astrocytes after infusion into the CNS. It is also well-known to those skilled in the art that astrocytes secrete factors that support the differentiation and normal function of CNS cells such as neurons. Thus, Kopen demonstrates that differentiated MSCs can be used to treat CNS diseases especially diseases where astrocytes and factors produced by them provide a therapeutic benefit for treating

that disease. Therefore, the results of Kopen et al. demonstrate that the specification as-filed is in fact enabled for the claimed invention because Kopen et al. arrived at the results predicted in the as-filed specification and demonstrated further reduction to practice of the present invention by using the same methods as those disclosed in the application.

Moreover, Hofstetter et al. demonstrates further post-filing reduction to practice in that MSC treatment improved recovery of an animal rendered paraplegic in an art-recognized model of spinal cord injury. Further, MSCs infused into the brain exhibited neuronal morphologies such as rounded cell bodies and distinct expression of nestin, vimentin and laminin, but demonstrated increased expression of NeuN, which is a neuronal specific marker. Such differentiated cells were termed "neuron-like MSC" and were believed to contribute in the repair process.

Chopp et al. teaches transplantation of MSCs into the spinal cord in an art-recognized rat model for spinal cord injury. Chopp demonstrates that MSCs injected into the rat spinal cord one week after a injury significantly improves functional outcome. Further, Chopp demonstrates that donor MSCs are present in the spinal cord and express neural protein markers (e.g. NeuN; see page 3004, Figure 2). Therefore, Chopp demonstrates successful treatment of spinal cord injury in an art-recognized animal model for human spinal cord injury.

The Examiner also contends that results obtained using animal models are unlikely to be applicable to human subjects. Applicants respectfully submit that art-recognized animal models of CNS disease have been used to develop effective therapies for human patients. For example, the rat model for parkinsonism was used to develop the use of L-DOPA for the treatment of this disease. The same rat model for parkinsonism was also used to develop therapy for the disease based on the infusion of fetal brain tissue.

One strategy for the present method is analogous to a therapy already in use for the treatment of parkinsonism, *i.e.*, implantation of neural tissue from the brains of human fetuses into the striatum of human patients. The neural tissue therapy has produced good results in some patients (*see, e.g.*, Brundin et al., 2000, Brain 123:1380-1390; Hagell et al., 2002, Nature Neuroscience 5:627-628).

Furthermore, the art-recognized animal model of spinal cord injury (SCI) was used to develop progesterone therapy for spinal cord injury in humans (Labombarda et al., 2002, J. Neurotrauma 19:343-355; Dumont et al., 2001, Clin. Neuropharmacol. 24:265-279).

Additionally, an art-recognized animal model for stroke was used (De Cristobal et al., 2001, J. Neurochem. 79:456-459) to develop drugs that prevent platelet aggregation for treatment of stroke in humans (Rezkalla et al., 2003, Clinical Med Res. 1:101-104).

These data demonstrate, contrary to the Examiner's assertions, that art-recognized animal models for Parkinson's disease, SCI and stroke have withstood the test of time as being extremely useful in developing new therapies for these diseases and for predicting the usefulness of therapies in human patients. Thus, the data demonstrate that these art-recognized animal models of CNS diseases are highly predictive of useful treatments for use in humans. For these reasons, the positive results obtained to treat Parkinson's disease, stroke, SCI and the like using MSCs in such animal models are applicable to human subjects.

Applicants respectfully submit that the specification supports the claims and that is all that is required under the patent statute to establish enablement. Otherwise, requiring human clinical data before a new therapy can be patented establishes an unprecedented and almost impossible barrier for developing any new therapies for scores of devastating human diseases.

For the reasons discussed above, claims 1-8 and 16-18, are amply enabled by the specification as filed, as further demonstrated by the extensive post-filing reduction to practice in art-recognized animal models, wherein the models have been demonstrated to be predictive of successful CNS treatment in humans. Therefore, the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement, should be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to claims 1-8 and 16-18 of the present application has been overcome or is now inapplicable, and that the claims are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of claims 1-8 and 16-18 is respectfully requested at the earliest possible date.

Respectfully submitted,

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October 24, 2005
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Enclosure: Petition for extension of time
Copy of references